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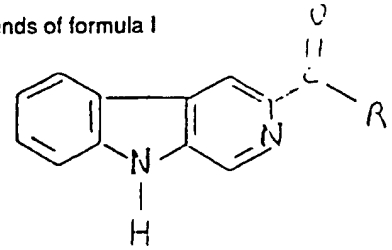
C2C CAA COS CRE CUK CWC C1173 C1174 C1175 C1360 C213 C22Y C220 C221 C225 C246 C247 C25Y C250 C252 C30Y C34Y C342 C35X C351 C355 C36Y C360 C362 C386 C396 C40Y C409 C43X C50Y C509 C52X C553 C584 C615 C623 C625 C652 C665 C675 C775 C777 C778 C80Y C802
U1S S1328 S2417

(56) Documents cited
None

(58) Field of search
UK CL (Edition J) C2C CUK CWC

(54) β-carboline derivatives and pharmaceutical uses thereof

(57) The invention relates to the compounds of formula I



(wherein R represents a cycloalkyl group containing 3 to 6 carbon atoms) and acid addition salts thereof, which may be used as minor tranquillisers and for the treatment of obesity or cognitive impairment.

Several precursor compounds are also claimed.

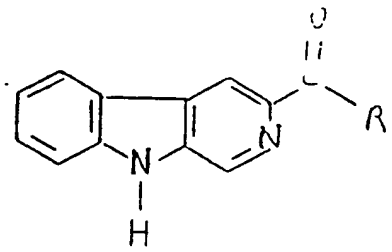
GB 2 209 032 A

10X51 957 Chemical Compounds 2209032

This invention relates to ß-carbolines substituted in the 3-position, to processes for their preparation and to their use as medicaments.

European Patent Application Nos. 30254, 54507 and 128415 describe a number of ß-carbolines substituted in the 3-position by various groups. None of these applications, however, describes ß-carbolines substituted in the 3-position by a cycloalkylcarbonyl group. It has now been found that such compounds possess very interesting properties; in particular, certain of these compounds possess remarkable affinity for the benzodiazepine receptor.

According to one aspect of the invention, there are provided compounds of formula I:



(I)

(wherein R represents a cycloalkyl group containing 3 to 6 carbon atoms) and acid addition salts thereof.

The term "cycloalkyl group containing 3 to 6 carbon atoms" as used herein means a cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl group.

It will be appreciated that, for pharmaceutical use, the salts referred to above will be physiologically acceptable salts, but other salts may find use, for example, in the preparation of compounds of formula I and physiologically acceptable salts thereof.

Preferred compounds according to the invention are as follows:

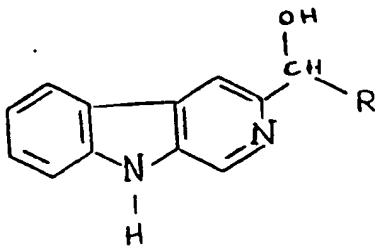
- (ß-carbolin-3-yl)-cyclopropylmethanone;

- (β-carbolin-3-yl)-cyclobutylmethanone;
- (β-carbolin-3-yl)-cyclopentylmethanone;

and acid addition salts thereof.

The compounds according to the invention may, for example, be prepared by the following processes, which processes constitute further features of the present invention:

a) Oxidation of a compound of formula II

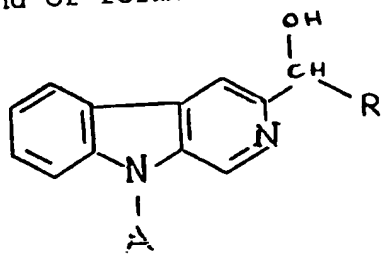


(II)

(wherein R is as defined above) and, if desired, subsequent salification of the compound of formula I thereby obtained.

The reaction is preferably carried out using manganese dioxide, nitric acid, ferric chloride or chromium oxide, in the presence of pyridine as oxidising agent, or by the Oppenauer method or by dehydrogenation in the presence of a copper catalyst.

The compounds of formula II may conveniently be prepared by removing the protecting group A from a compound of formula III

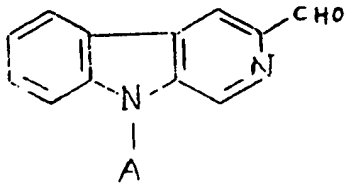


(III)

wherein R is as defined above and A represents an appropriate protecting group, for example, a trimethylsilyl group.

If, in the above reaction, the protecting group used is a trimethylsilyl group, this is preferably removed by means of an aqueous or weakly acidic solution, or by a source of fluoride ion such as, for example, tetrabutylammonium fluoride in tetrahydrofuran.

The compounds of formula III may conveniently be prepared by reacting a compound of formula IV



(IV)

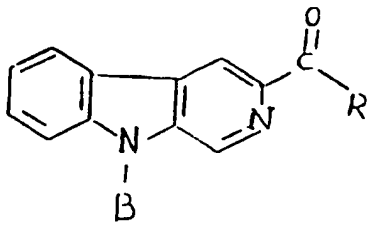
(wherein A is as defined above) with an organometallic derivative of formula

M-R (V)

wherein M represents an alkali metal atom (eg a lithium atom) or a group -Mg-Hal (in which Hal represents a chlorine, bromine or iodine atom) and R is as defined above.

The reaction is preferably effected under anhydrous conditions, and in the presence of an organic solvent such as tetrahydrofuran.

b) Removal of a protecting group B from a compound of formula VI



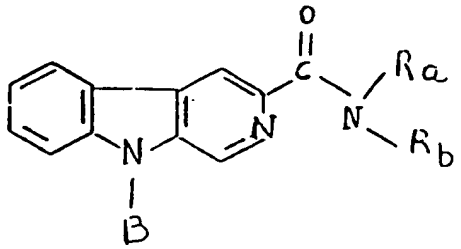
(VI)

wherein B represents an appropriate protecting group, for example, a paratoluenesulphonyl group,

and R is as defined above and, if desired, subsequent salification of the compound of formula I thereby obtained.

If, in the above reaction, the protecting group used is a paratoluenesulphonyl group, this group is preferably removed by means of an alkaline solution such as potassium hydroxide.

The compounds of formula VI may conveniently be prepared by reacting a compound of formula VII



(VII)

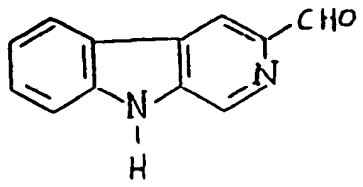
(wherein B is as defined above, R_a represents an alkyl group containing 1 to 3 carbon atoms and R_b represents an alkyl group containing 1 to 3 carbon atoms or an alkoxy group containing 1 to 3 carbon atoms) with an organometallic derivative of formula V:

M-R (V)

wherein M and R are as defined above.

The reaction is preferably effected under anhydrous conditions, and in the presence of an organic solvent such as tetrahydrofuran.

The compounds of formula IV may conveniently be prepared by reacting a compound of formula VIII



(VIII)

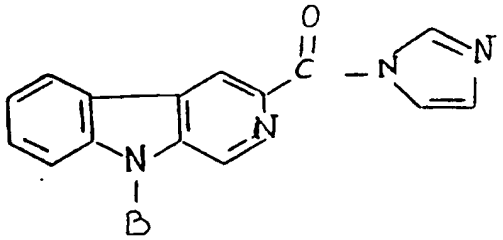
with an appropriate reagent serving to introduce the protecting group A, for example trimethylsilyl chloride.

If the reagent used is trimethylsilylchloride, the reaction is preferably effected by mixing, under an inert gas, a solution of β-carboline-3-carboxylaldehyde in hexamethylphosphoramide with sodium hydride and then adding the trimethylsilyl chloride.

β-Carboline-3-carboxylaldehyde may be prepared, for example, as described in J.Med. (1982) 25 (9) 1081.

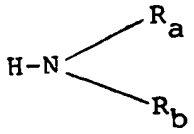
The compounds of formula VII may be prepared by the following processes, which processes constitute still further features of the present invention:

Reaction of a compound of formula IX



(IX)

(wherein B is as defined above) with a compound of formula X



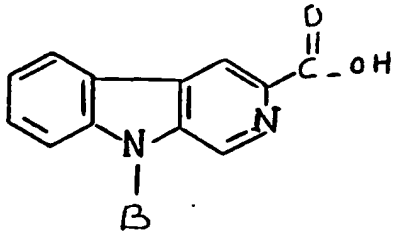
(X)

wherein R_a and R_b are as defined above or an acid addition salt thereof.

The compound of formula X or acid addition salt thereof used is preferably dimethylamine or

N-methyl-O-methylhydroxylamine hydrochloride.

The compounds of formula IX may conveniently be prepared by reacting a compound of formula XI

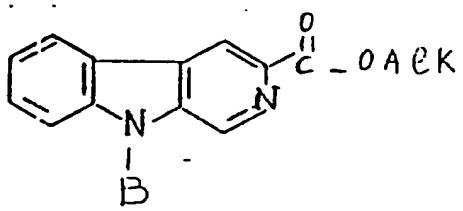


(XI)

(wherein B is as defined above) with carbonyl-dimidazole.

The reaction is preferably effected in the presence of an organic solvent such as dimethylformamide.

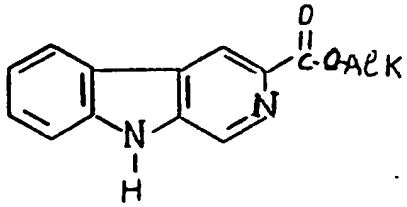
The compounds of formula XI may conveniently be prepared by saponifying a compound of formula XII



(XII)

wherein B is as defined above and Alk represents an alkyl group containing 1 to 3 carbon atoms.

The compounds of formula XII may conveniently be prepared by reacting a compound of formula XIII



(XIII)

(wherein Alk is as defined above) with an appropriate reagent serving to introduce the protecting group B, for example, paratoluenesulfonyl chloride.

If the reagent used is paratoluenesulfonyl

chloride, the reaction is preferably effected in the presence of an amine such as 4-dimethylaminopyridine or triethylamine, in the presence of an anhydrous organic solvent such as dichloromethane.

The compounds of formula XIII may be prepared as described in J. med. Chem (1982) 25 (9) 1081.

The acid addition salts of the compounds of formula I may advantageously be prepared by reacting, in approximately stoichiometric proportions, an inorganic or organic acid with the compound of formula I. Suitable acids include, for example, inorganic acids such as hydrochloric, hydrobromic, sulphuric and phosphoric acid and organic acids such as formic, acetic, propionic, benzoic, maleic, fumaric, succinic, tartric, citric, oxalic, glyoxylic and aspartic acid, and alkanesulphonic acids such as methane sulphonic and ethane sulphonic acid, and arylsulphonic acids such as benzene sulphonic acid and paratoluene sulphonic acid.

Pharmacological Activity

As mentioned above, the compounds of formula I are agents which interact with benzodiazepine receptors in the brain, and some of them may be useful as minor tranquillisers, as benzodiazepine inverse agonists or antagonists and for the treatment of obesity or cognitive impairment. Screening for benzodiazepine receptor binding (FRB) was carried out by the method described in published UK Patent Application No. 2,128,989 A. The values given in Table 2 are expressed in terms of IC_{50} (nM).

The affinity of the compounds for the benzodiazepine receptor was assessed using the radioligand [^{3}H]-flunitrazepam by modification of the original radioceptor binding method of SQUIRES and BRAESTRUP (Nature, 1977, 266, 732). The values given in Table I below refer to the nanomolar concentration

of test drug which inhibited the specific binding of 0.6 nM [^{3}H]-flunitrazepam to rat forebrain membrane preparations by 50% (IC_{50} nM).

TABLE I

Compound of Example	F R B
1	0.7
2	1000
3	4.0
4	7.9

Benzodiazepine inverse agonist properties are indicated by the following tests.

a) The ability of the compounds to induce twitch in the hyoidal muscle of rats was studied according to the method of V.W. James and R.C. Gardner (European J. Pharmacol. (1985) 113 233).

TABLE II

Compound of Example	Hyoidal Twitch mg/kg
1	1-10 i.p. ++
	1 i.v. +++
2	-
3	5 i.v. (ant) +
4	20 i.p. (ant)

(ant. signifies that the compound antagonises a classical benzodiazepine)

b) Potentiation of seizures induced by subcutaneous injection of leptazol to CD_1 mice

A dose of leptazol is selected to give 10-20% tonic seizures in untreated CD_1 mice. Active compounds increase the percentage of tonic seizures and the ED_{50} is calculated by the method of Lichfield and Wilcoxon (J. Pharmacol Exp. Ther. (1949) 96, 99).

Compound of Example 1 : ED_{50} = 0.45 mg/kg i.p. (30 mins pretest)

2 > 100 mg/kg i.p.

3 > 100 mg/kg i.p.

4 > 100 mg/kg i.p.

The pharmaceutical compositions according to the present invention are thus of use in the treatment of anxiety, cognitive dysfunction, obesity or cognitive impairment. Thus, the present invention provides compounds of formula I and physiologically acceptable acid addition salts thereof for use in therapy.

According to a yet further feature of the present invention there are provided pharmaceutical compositions containing, as active ingredient, at least one compound of formula I as defined above or a physiologically acceptable acid addition salt thereof in association with one or more pharmaceutical carriers and/or excipients. Preferred as active ingredients are the following compounds of formula I:

- (β-carbolin-3-yl)-cyclopropylmethanone.
- (β-carbolin-3-yl)-cyclobutylmethanone.
- (β-carbolin-3-yl)-cyclopentylmethanone.

For pharmaceutical administration the compounds of formula I may be incorporated into the conventional preparations in either solid or liquid form, optionally in combination with other active ingredients. The compositions may, for example, be presented in a form suitable for oral, rectal or parenteral

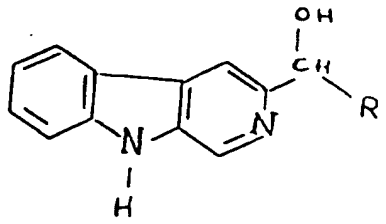
administration. Preferred forms include, for example, plain tablets, coated tablets, capsules (including gelatin capsules), granules, suppositories and solutions (e.g. for injection).

The active ingredient may be incorporated in excipients customarily employed in pharmaceutical compositions such as, for example, talc, gum arabic, lactose, starch, magnesium stearate, cocoa butter, aqueous or non-aqueous vehicles, fatty substances of animal or vegetable origin, paraffin derivatives, glycols, various wetting, dispersing or emulsifying agents and/or preservatives.

Advantageously the compositions may be formulated as dosage units, each unit being adapted to supply a fixed dose of active ingredient. Suitable dosage units for adults contain from 0.1 mg to 100 mg, preferably from 0.1 mg to 20 mg, of active ingredient. The oral daily dosage, which may be varied according to the compound used, the subject treated and the complaint concerned, may, for example, be from 0.1 mg to 200 mg per day in adults.

According to a still further aspect of the invention, there are provided the following intermediate compounds:

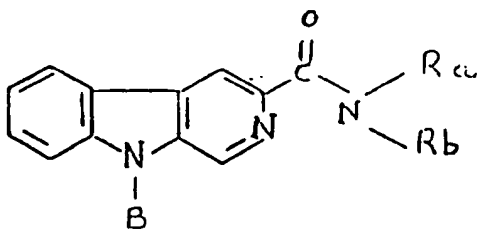
- the compounds of formula II



(II)

wherein R is as defined above,

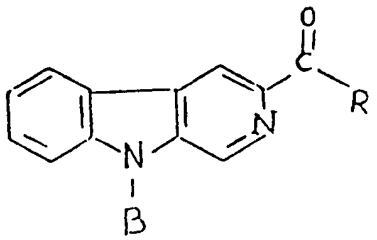
- the compounds of formula VII:



(VII)

wherein B, R_a and R_b are as defined above,

- the compounds of formula VI:



(VI)

wherein B and R are as defined above.

The following non-limiting Examples serve to illustrate the present invention more fully.

Example 1 : (beta-carbolin-3-yl)-cyclopropyl-methanone.

Step A : (Beta -Carbolin-3-yl) cyclopropylmethanol

A solution of (Beta-carboline-3-carboxaldehyde (1.8g, 9.2mmol) in hexamethylphosphoramide (10ml) was stirred under nitrogen with sodium hydride (80% oil dispersion) (0.31g, 10.3mmol) at 20° for 15 mins. Freshly distilled trimethylsilylchloride (2.5ml, 19.7mmol) was added and the mixture stirred at 20°C for 10 mins. A solution of cyclopropylmagnesium bromide prepared from magnesium (1.6g) and cyclopropyl bromide (7.2g) in tetrahydrofuran (15ml) was added dropwise with cooling. The mixture was stirred at ambient temperature for 18hrs and quenched with saturated ammonium chloride solution. The precipitated product was filtered, dissolved in chloroform, dried over magnesium sulphate and evaporated to give (Beta-carbolin-3yl) cyclopropylmethanol as a buff coloured solid (1.58g, 74% yield) mpt 205-7° (EtOH).

IR (KBr) 3420, 3150, 1632, 1501, 1469, 1337, 1251cm^{-1}

NMR ($CDCl_3/CD_3OD$)S 8.71(s); 8.12(d); 8.07(s); 7.50(m, 2H); 7.28(m); 4.23(d, CH-O); 1.30(m, 1H, cyclopropyl); 0.60(m, 4H, cyclopropyl).

Step B : (Beta-Carbolin-3-yl)-cyclopropylmethanone

(Beta-Carbolin-3-yl)- cyclopropylmethanol (1.47g) in chloroform (500ml) was stirred under reflux for 3hrs with manganese dioxide (5.5g). The mixture was filtered hot and evaporated under reduced pressure to give (Beta-Carbolin-3-yl)- cyclopropylmethanone as buff coloured solid (1.3g, 88% yield) mpt 225-7° (EtOH).

IR (KBr) 3240, 1660, 1591, 1386, 1248cm^{-1}

NMR (CD_3OD)S 8.91(s); 8.80(s); 8.24(d); 7.51(m, 2H); 7.31(m); 3.58(m COCH); 1.15(m, 4H, cyclopropyl).

$C_{15}H_{12}N_2O$ requires C, 76.25%; H, 5.12%; N, 11.86%.
found C, 76.28%; H, 5.17%; N, 11.76%.

Example 2 : (Beta-carbolin-3-yl)-cyclohexylmethanone.

Step A : Methyl 9-(p-toluenesulphonyl)-Beta-carboline-3-carboxylate

Méthyl beta-carboline-3-carboxylate (12.5g, 55.3mmol), p-toluenesulphonyl chloride (10.85, 56.9mmol), 4-dimethylaminopyridine (2.02g 16.6mmol) and triethylamine (19.3ml, 0.138mmol) in dry dichloromethane (700ml) was refluxed for $2^1/_4$hrs. The resulting solution was cooled, washed with dil aq. HCl (twice) and water (twice), dried $MgSO_4$, filtered and evaporated. The product was purified by flash chromatography ($SiO_2/CHCl_3$) and the resulting solid triturated with ether, filtered, washed with ether and dried under vacuum to give methyl 9-(p-toluenesulphonyl)-beta-carboline-3-carboxylate as a white powder (18.4g, 87% yield) mpt 176-179°C.

IR (KBr) 1720, 1383, 1294, 1176, 980cm^{-1}.

NMR ($CDCl_3$)S 9.74(d); 8.71(d); 8.39(d.d); 8.06(d.d);
7.76(d, 2H, tosyl); 7.69(m); 7.48(m); 7.15(d, 2H, tosyl);
4.06(s, 3H, OMe); 2.27(s, 3H, tosylMe).

Step B : 9-(p-toluenesulphonyl)-beta-carboline-3-carboxylic acid

A suspension of methyl 9-(p-toluenesulphonyl) ~~-beta-carboline-3-carboxylate~~ (18.4g, 48.3mmol) in acetone (750ml) was treated with 0.25M aq NaOH solution (203ml, 50.7mmol). The resulting solution was stirred at ambient temperature for 2hrs then acidified to pH=3 (dilute aq HCl) to give a fine precipitate. This was filtered, washed with water and dried under vacuum over P_2O_5 at 70°C to give 9-(p-toluenesulphonyl)-beta-carboline-3-carboxylic acid as a white powder (17.0g; 96% yield) mpt 228-232°C.

IR (KBr) 3200-2400(br), 1770-1680(br), 1450, 1380, 1257, 1175cm^{-1}.

Step C : N,N-dimethyl-9-(p-toluenesulphonyl)-beta-carboline-3-carboxamide

To stirred solution of 9(p-toluenesulphonyl)-beta-carboline-3-carboxylic acid (17.0g, 46.4mmol) in dry DMF (400ml) was added carbonyl diimidazole (15.0g, 92.8mmol); and the solution stirred at ambient temperature for 2hrs before saturating with dimethylamine (gas) for 5 min and stirring for a further 1hr. The resulting solution was diluted with ethyl acetate and washed with water (x4). The organic phase was dried ($MgSO_4$), filtered and evaporated to give a solid which was triturated with ether containing a little ethyl acetate. The resultant solid was filtered, washed with ether and dried under vacuum (P_2O_5/70°C) to give N,N-dimethyl-9-(p-toluenesulphonyl)-beta-carboline-3-carboxamide as a buff solid (16.1g, 88% yield) mpt 184-185°C

IR (KBr) 1640, 1443, 1388, 1178 and 980cm^{-1}.

NMR ($CDCl_3$)S 9.58(d); 8.38(d.d); 8.25(d); 8.00(d.d); 7.73(d, 2H); 7.68(m); 7.46(m); 7.15(d, 2H); 3.18(s, 6H, NMe_2); 2.28(s, 3H).

Step D : Cyclohexyl (9-(p-toluenesulphonyl)beta-carbolin-3-yl) methanone

To a stirred solution of N,N-dimethyl-9-(p-toluenesulphonyl)-beta-carboline-3-carboxamide (2.0g, 5.1mmol) in dry THF (150ml) at 0°C under N_2 was added dropwise, over a period of 30 mins cyclohexylmagnesium bromide (4.7ml, 0.44M in THF, 20.7mmol). The resulting solution was stirred at 0°C for 1hr then poured into dil aq ammonium chloride solution and extracted with ethyl acetate. The organic phase was washed with H_2O twice, dried ($MgSO_4$), filtered and evaporated and the product purified by flash chromatography (SiO_2/CH_2Cl_2). The solid recovered was triturated with ether, filtered, washed with ether and dried under vacuum to give cyclohexyl (9-(p-toluenesulphonyl)-beta-carbolin-3-yl)methanone as a white solid (1.6g, 73% yield) mpt 181-184°C.

IR (KBr) 2930, 1688, 1448, 1380, 1175, 979cm^{-1}.

NMR ($CDCl_3$)S 9.67(d); 8.61(d); 8.37(d.d); 8.05(d.d); 7.79(d, 2H); 7.68(m); 7.46(m); 7.17(d, 2H); 4.00(br.m, 1H, COCH); 2.30(s,3H); 1.15-2.05 (br.m, 10H, cyclohexyl)

Step E : (Beta-Carbolin-3-yl)-cyclohexylmethanone

A suspension of cyclohexyl (9-(p-toluenesulphonyl)- beta-carbolin-3-yl)methanone (1.6g, 3.7mmol) in dry methanol (80ml) was treated with KOH (623mg, 11.1mmol), then heated at 60°C for $1^1/_2$hrs. The resulting solution was cooled and the product crystallized out. The solid was filtered off, washed with ether and dried under vacuum to give cyclohexyl (beta-carbolin-3-yl)-methanone (900mg, 87% yield) as a white crystalline solid, mpt 227-230°C.

IR (KBr) 3250, 2930, 1660, 1625, 1590, 1200cm^{-1}.

NMR (DMSO-d_6)S 9.01(d); 8.83(d); 8.40(d.d); 7.63(m, 2H); 7.32(m); 4.02(br.m); 1.2-1.9(br.m, 10H, cyclohexyl).

$C_{18}H_{18}N_2O$ requires C, 77.67%; H, 6.52%; N, 10.06%.
found C, 77.58%; H, 6.61%; N, 10.02%.

Alternative preparation

Cyclohexyl [9-(p-toluenesulphonyl)-beta-carbolin-3-yl] methanone was prepared from methyl N-methyl-9-(p-toluenesulphonyl)-beta-carbolin-3-carbohydroxamate by a similar process to that described in step D.

Preparation of Methyl N-methyl 9-(p-toluene sulphonyl)-Beta-carboline -3-carbohydroxamate.

Prepared from the acid in a similar manner to Step C using N-methyl-O-methylhydroxylamine hydrochloride (2eq) in place of dimethylamine. The product was purified by flash chromatography ($SiO_2/CHCl_3$) and the resulting solid triturated with ether, filtered, washed with ether and dried under vacuum to give methyl N-methyl-9-(p-toluenesulphonyl)- beta-carboline-3-carbohydroxamate, (708mg, 90% yield) as a white crystalline solid; mpt 148-50°C.
IR (KBr) 1641, 1618, 1148, 1375, 1175, 980cm^{-1}.
NMR ($CDCl_3$)S 9.62(d); 8.38(d); 8.30(d); 8.02(d); 7.75(d, 2H); 7.68(m); 7.46(m); 7.16(d, 2H); 3.84(s, 3H, OMe); 3.50(s, 3H, NMe); 2.30(s, 3H, tosylMe).
$C_{14}H_{13}N_3O_2$ requires C, 65.87%; H, 5.13%; N, 16.46%
found C, 65.79%; H, 5.23%; N, 16.34%

Example 3 : (Beta-carbolin-3-yl) cyclobutylmethanone

Using a process similar to that used at step D and E of example 2 but starting from the cyclobutyl magnesium bromide the (Beta-carbolin-3-yl) cyclobutylméthanone was prepared.

mpt 218-220°C

IR (KBr) 3270, 1665, 1625, 1590, 1375, 1255cm^{-1}.

NMR (DMSO-d_6)S 8.96(d); 8.55(d); 8.41(m); 7.68(m); 7.61(m); 7.32(m); 4.58(m); 2.28(m, 2H); 2.07(m); 1.84(br.m, 6H).

$C_{16}H_{14}N_2O$ requires C, 76.78%; H, 5.64%; N, 11.19%.
found C, 76.73%; H, 5.81%; N, 11.09%.

Example 4 : (Beta-carbolin-3-yl) cyclopentylmethanone

Using a process similar to that used at step D and E example 2 but starting from the cyclopentyl magnesium bromide the(Beta-carbolin-3-yl) cyclopentyl methanone was prepared.

mpt 219-220°C

IR (KBr) 3270, 1663, 1625, 1590, 1374, 1251cm^{-1}.

NMR (DMSO-d_6)S 9.00(d); 8.86(d); 8.41(m); 7.68(m); 7.62(m); 7.33(m); 4.39(br.m); 1.94(br.m, 2H); 1.75(br.m, 6H).

$C_{17}H_{16}N_2O$ requires C, 77.25%; H, 6.10%; N, 10.60%.
found C, 77.02%; H, 6.20%; N, 10.51%.

Example 5

Tablets were prepared according to the formulation:

- Compound of Example 1 : 20 mg
- Excipient q.s. for one tablet up to : 150 mg

(Details of the excipient: lactose, starch, talc, magnesium stearate).

Example 6

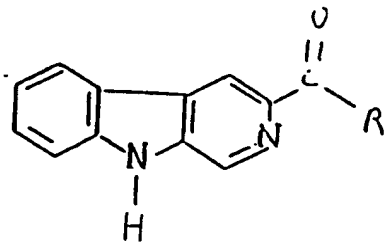
Tablets were prepared according to the formulation:

- Compound of Example 3 : 20 mg
- Excipient q.s. for one tablet up to : 150 mg

(Details of the excipient: lactose, starch, talc, magnesium stearate).

Claims:

1. Compounds of formula (I)



(I)

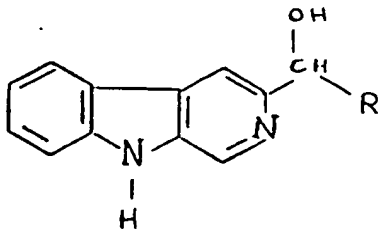
(wherein R represents a cycloalkyl group containing 3 to 6 carbon atoms) and acid addition salts thereof.

2. -(β-Carbolin-3-yl)-cyclopropylmethanone;
-(β-carbolin-3-yl)-cyclobutylmethanone;
-(β-carbolin-3-yl)-cyclopentylmethanone;
and acid addition salts thereof.

3. Physiologically acceptable acid addition salts of compounds of formula (I) as defined in claim 1.

4. Compounds as claimed in claim 1 as herein specifically diclosed in any one of Examples 1 to 4.

5. A process for the preparation of a compound of formula (I) as defined in claim 1 which comprises oxidation of a compound of formula II

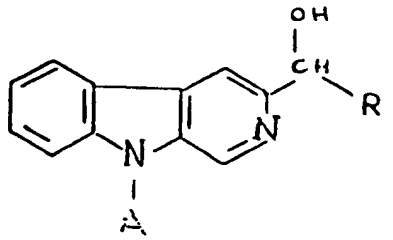


(II)

(wherein R is as defined in claim 1.)

6. A process as claimed in claim 5 wherein the reaction is carried out using manganese dioxide, nitric acid, ferric chloride or chromium oxide, in the presence of pyridine as oxidising agent, or by the Oppenauer method or by dehydrogenation in the presence of a copper catalyst.

7. A process as claimed in claim 5 or claim 6 wherein the compound of formula II is prepared by removing the protecting group A from a compound of formula III

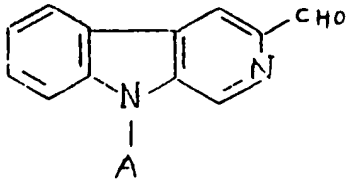


(III)

wherein R is as defined in claim 1 and A represents an appropriate protecting group.

8. A process as claimed in claim 7 wherein in the compound of formula III, A represents a trimethylsilyl group and the group A is removed by means of an aqueous or weakly acidic solution or by a source of fluoride ions.

9. A process as claimed in claim 7 or claim 8 wherein the compound of formula III is prepared by reacting a compound of formula IV



(IV)

(wherein A is as defined in claim 7) with an organometallic derivative of formula

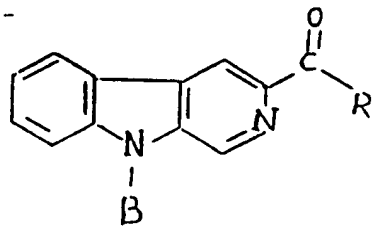
M-R (V)

wherein M represents an alkali metal atom or a group -Mg-Hal (in which Hal represents a chlorine, bromine or iodine atom) and R is as defined in claim 1.

10. A process as claimed in claim 9 wherein the reaction between the compound of formula IV and the compound of formula V is effected under anhydrous conditions,

and in the presence of tetrahydrofuran.

11. A process for the preparation of a compound of formula I as defined in claim 1 which comprises removal of a protecting group B from a compound of formula VI

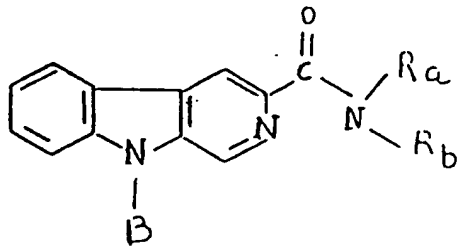


(VI)

wherein B represents an appropriate protecting group and R is as defined in claim 1.

12. A process as claimed in claim 11 wherein in the compound of formula VI, B represents a paratoluenesulphonyl group and the group B is removed using potassium hydroxide.

13. A process as claimed in claim 11 or claim 12 wherein the compound of formula VI is prepared by reacting a compound of formula VII



(VII)

(wherein B is as defined in claim 11, R_a represents an alkyl group containing 1 to 3 carbon atoms and R_b represents an alkyl group containing 1 to 3 carbon atoms or an alkoxy group containing 1 to 3 carbon atoms) with an organometallic derivative of formula V:

M-R (V)

wherein M is as defined in claim 9 and R is as defined in claim 1.

14. A process as claimed in claim 13 wherein the reaction between the compound of formula VII and the compound of formula V is effected under anhydrous conditions, and in the presence of an organic solvent such as tetrahydrofuran.

15. A process as claimed in any one of claims 5 to 14 wherein a compound of formula I initially obtained is subsequently converted into an acid addition salt thereof and/or an acid addition salt of a compound of formula I is subsequently converted into a compound of formula I.

16. A process for the preparation of compounds as claimed in claim 1 substantially as herein described.

17. A process for the preparation of compounds as claimed claim 1 substantially as herein described in any one of Examples 1 to 4.

18. Compounds of formula I as defined in claim 1 and acid addition salts thereof wherever prepared by a process as defined in any one of claims 5 to 17.

19. Compounds as claimed in any one of claims 1 to 4 for use in therapy.

20. The use of a compound as claimed in any one of claims 1 to 4 for the manufacture of a medicament for the treatment of anxiety, cognitive dysfunction, obesity or cognitive impairment.

21. Pharmaceutical compositions comprising, as active ingredient, at least one compound of formula I as defined in claim 1 or a physiologically acceptable salt thereof in association with a pharmaceutical carrier and/or excipient.

22. Compositions as claimed in claim 21 wherein the active ingredient comprises a compound as defined in any one of claims 2 to 4.

23. Compositions as claimed in claim 21 or claim 22 in the form of dosage units.

24. Compositions as claimed in claim 23 wherein each dosage unit contains from 0.1mg to 100mg of active ingredient.

25. Compositions as claimed in claim 24 wherein each dosage unit contains from 0.1mg to 20 mg of active ingredient.

26. Pharmaceutical compositions as claimed in claim 21 substantially as herein described.

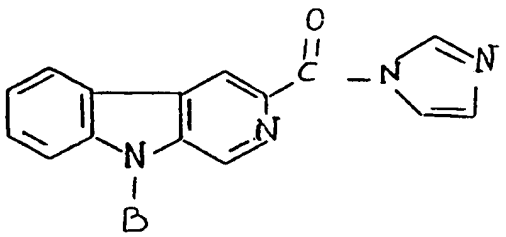
27. Pharmaceutical compositions substantially as herein described in Example 5 or Example 6.

28. Compounds of formula II as defined in claim 5.

29. Compounds of formula VII as defined in claim 13.

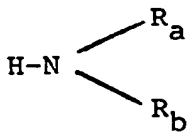
30. Compounds of formula VI as defined in claim 11.

31. A process for the preparation of a compound of formula VII as defined in claim 13 which comprises reaction of a compound of formula IX



(IX)

(wherein B is as defined in claim 11) with a compound of formula X

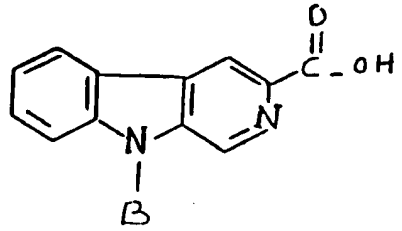


(X)

wherein R_a and R_b are as defined in claim 13 or an acid addition salt thereof.

32. A process as claimed in claim 31 wherein the compound of formula X or acid addition salt thereof used is dimethylamine or N-methyl-O-methylhydroxylamine hydrochloride.

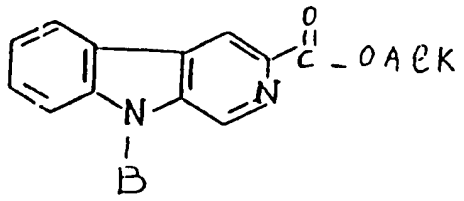
33. A process as claimed in claim 31 or claim 32 wherein the compound of formula IX is prepared by reacting a compound of formula XI



(XI)

(wherein B is as defined in claim 11) with carbonyldiimidazole.

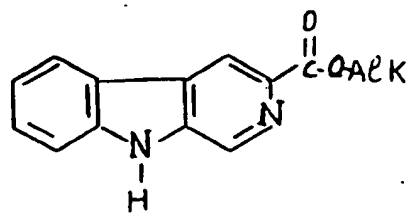
34. A process as claimed in claim 33 wherein the compound of formula XI is prepared by saponifying a compound of formula XII



(XII)

wherein B is as defined in claim 11 and Alk represents an alkyl group containing 1 to 3 carbon atoms.

35. A process as claimed in claim 34 wherein the compound of formula XII is prepared by reacting a compound of formula XIII



(XIII)

(wherein Alk is as defined in claim 34) with an appropriate reagent serving to introduce the protecting group B (wherein B is as defined in claim 11).

36. Each and every novel method, process, compound, and composition herein disclosed.

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